

Urotensin II level is elevated in inflammatory bowel disease patients

Yan Zhang, Guo-Xun Chen

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Yan Zhang, Department of Gastroenterology, Affiliated Puren Hospital of Wuhan University of Science and Technology, Wuhan 430081, Hubei Province, China

Guo-Xun Chen, Department of Nutrition, The University of Tennessee, Knoxville, TN 37996, United States

Corresponding author: Guo-Xun Chen, PhD, Associate Professor, Research Scientist, Department of Nutrition, The University of Tennessee, Room 229, Jessie Harris Building, 1512 West Cumberland Avenue, Knoxville, TN 37996, United States. gchen6@utk.edu

Abstract

It was reported that the urotensin II (U-II) level in inflammatory bowel disease (IBD) patients are significantly higher than in controls. To provide future guidance for the management of cardiovascular risk factors in IBD patients, the sample size of the current study appears to be limited, and more clinical samples to compare U-II levels in IBD patients and controls are needed. This will clarify the possible roles of inflammation factors and related signaling pathways (like EPK1/2, NF- κ B and Rho/ROCK) in the pathophysiology of IBD. Therefore, large multicenter studies should be done to confirm the findings and underlying mechanisms in the future.

Key Words: Inflammatory bowel disease; Urotensin II; Inflammatory factors; High sensitivity C reactive peptide

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Core Tip: An observational report showed that the level of urotensin II (U-II) in inflammatory bowel disease (IBD) patients was significantly increased compared with that in controls. The authors also reported that blood U-II level was positively correlated with high-sensitivity C-reactive protein, and severe endoscopic features of the disease. This study provides us with a new role of U-II in IBD, which warrants larger, multicenter clinical and basic studies to determine the mechanisms by which U-II triggers inflammatory responses and activates signaling pathways (EPK1/2, NF- κ B and Rho/ROCK).

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TO THE EDITOR

We read the observational study reported by Alicic *et al*[1], who have convincingly shown the role of elevated urotensin II (U-II) level in patients with inflammatory bowel disease (IBD). IBD comprising Crohn's disease (CD) and ulcerative colitis (UC) is a multifactorial condition of relapsing chronic inflammation in the gastrointestinal tract with an unpredictable course[2]. In addition, extraintestinal manifestations of IBD cardiovascular risk factors occur frequently and contribute to morbidity and reduced quality of life[3-5].

U-II is a peptide ligand that acts as a potent vasoconstrictor, which was originally discovered four decades ago. The vasoconstriction activity of U-II is 10-fold more potent than that of endothelin-1[6]. Most studies of U-II have been conducted to understand its role in the development of cardiovascular diseases[7]. A growing number of scholars have recognized the links of U-II levels with malignant lesions associated with the liver, pancreas and gut[8]. Whether U-II participates in the initiation and progress of IBD has always intrigued contemporary gastroenterologists. This observational study reported the potential relationship of U-II and IBD, which provides the field with new knowledge and attracted our attention.

Alicic *et al*[1] compared the blood level of U-II in IBD patients and healthy controls, and investigated the association of U-II levels with the anthropometric, clinical and biochemical parameters. The study included 50 adult patients with prediagnosed IBD (24 with UC and 26 with CD) and 50 healthy, age- and gender-matched controls. IBD patients had significantly higher U-II level than control subjects had. Significant positive correlations between serum U-II level and high-sensitivity C-reactive protein (hsCRP) level, UC Endoscopic Index of Severity and Simple Endoscopic Score for CD were observed. Whether these clinical data imply the involvement of U-II in the inflammatory responses and disease outcomes of IBD patients remains to be confirmed.

The action of U-II is mediated by U-II receptor (UTR). UTR is also called GPR14, which is a G-protein-linked receptor[9]. Both U-II and UTR can be found in various cells of the cardiovascular, pulmonary and central nervous systems, kidneys, and other metabolic organs and tissues. The binding of U-II as a ligand activates UTR, which mobilizes calcium in the cytoplasm, induces proliferation of smooth myocytes, and triggers inflammation[10,11]. As expected, the level of inflammatory factor hsCRP in IBD patients is significantly higher than that in healthy controls.

The study by Alicic *et al*[1] is the first clinical study to investigate blood U-II level in both UC and CD patients. However, limitations can be seen, which could bolster the authors' conclusions if resolved: (1) This single center study only had 50 subjects each in the IBD and control groups. If more institutions were included in a multicenter investigation and more patients were recruited, the conclusions would become more convincing and relevant. Therefore, large multicenter studies are anticipated in the future; and (2) the results showed that elevation of blood U-II level was associated with disease development and progression, and attributed to the inflammation mediated by hsCRP. However, the levels of other inflammatory factors were not measured (*e.g.*, interleukin-6, interleukin-8, and tumor necrosis factor- α). Their level and involvement in the elevated U-II concentration and inflammatory responses in those patients should be clarified. Regarding the mechanisms, it is possible that U-II as a ligand activates pathways that stimulate the release of inflammatory effectors, such as the cytokines listed above. These cytokines may potentially activate signaling pathways consisting of EPK1/2, NF- κ B and Rho/ROCK, which regulate a variety of downstream inflammatory responses[12-14]. Whether those cytokines and U-II act against each other or in concert to form a system influencing the host inflammation status remains to be answered. In the future, gastroenterologists should investigate how U-II interacts with other inflammatory mediators, and how U-II modifies those signaling pathways to potentiate IBD severity in various *in vivo* and *in vitro* systems. In so doing, more results could be collected and analyzed, which are needed to form theoretical and practical evidence to guide prevention and treatment of cardiovascular complications in IBD. Additionally, antagonists to the UTR activation system could also be developed, which may counteract any detrimental effects due to increased level of U-II in patients with IBD.

FOOTNOTES

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Country/Territory of origin: United States

ORCID number: Yan Zhang 0000-0002-0620-5803; Guo-Xun Chen 0000-0001-6226-4050.

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